ACUTE TOXICITY SUMMARY

ACROLEIN

CAS Registry Number: 107-02-8

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**0.19 μg/m³**
Critical effect(s)	eye irritation in healthy human volunteers
Hazard Index Target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless liquid
Molecular formula	C_3H_4O
Molecular weight	56.1
Density	0.843 g/cm^3 @ 20°C
Boiling point	53°C
Melting point	-87°C
Vapor pressure	220 mm Hg @ 20°C
Flashpoint	-26°C
Explosive limits	2.8% - 31% by volume
Solubility	soluble in ethanol, diethyl ether, and up to 20% w/v in water
Odor threshold	0.5 ppm
Metabolites	glycidaldehyde, acrylic acid
Conversion factor	1 ppm in air = 2.3 mg/m³ @ 25° C

III. Major Uses or Sources

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water-treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein.

IV. Acute Toxicity to Humans

Exposure to 1 ppm (2.3 mg/m³) for 5 minutes causes lacrimation and irritation of the eyes, nose, and throat (IARC: Fassett, 1962). At a concentration of 7 mg/m³, acrolein causes severe lacrimation and irritation of the mucous membranes of the respiratory tract (Prentiss, 1937). A 10-minute exposure to 350 mg/m³ acrolein was lethal (Prentiss, 1937). A case report of respiratory failure and death in individuals exposed to vapors from overheated frying pans

containing fat and food items implicated acrolein as the principal toxicant (Gosselin *et al*. 1979). The lowest observed adverse effect level (LOAEL) for eye irritation in healthy human volunteers is exposure to 0.14 mg/m³ (0.06 ppm) acrolein for five minutes (Darley *et al*., 1960).

Prolonged treatment of cancer patients with cyclophosphamide can result in hemorrhagic cystitis. The bladder toxicity is due to the formation of acrolein as a metabolite and may be prevented by co-administration of 2-mercaptoethane sulfonate (Brock *et al*., 1979).

There is inadequate direct evidence for carcinogenicity of acrolein in experimental animals or in humans (IARC, 1985). However, a metabolite of acrolein, the reactive epoxide glycidaldehyde, has been shown to be mutagenic and carcinogenic in mice and rats. Therefore, acrolein has been designated a Group C substance, with possible human carcinogenic potential (U.S.EPA, 1987).

Predisposing Conditions for Acrolein Toxicity

Medical: Persons with pre-existing eye, skin, respiratory, allergic, asthmatic or heart diseases might be at increased risk due to acrolein exposure. Individuals with cystic fibrosis or asthma should be excluded from acrolein exposure (Reprotext, 1999).

Chemical: Cancer patients treated with cyclophosphamide could be at increased risk because acrolein is a metabolite of cyclophosphamide (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The LC_{50} for inhalation of acrolein in rats is 300 mg/m³ for a 30-minute exposure (Fassett, 1963). An LC_{50} of 152 mg/m³ is reported in mice for a 6-hour exposure (Philippin *et al*., 1970). An LC_{50} of 58 mg/m³ for a four-hour exposure is reported for hamsters (Kruysse, 1971). No mortality was observed in 8 rats exposed to 100 mg/m³ acrolein for 30 minutes, although heavy lacrimation and nasal secretion were reported (NTIS, 1981). An initial 35% decrease in liver alkaline phosphatase (AP) activity, followed by a 200% increase in AP activity over controls, was seen in rats exposed to 10 mg/m³ for 24 hours (NTIS, 1981). In guinea pigs, exposure to 39.6 mg/m³ for 1 hour resulted in no changes in respiratory rate, minute volume, or airway resistance (NTIS, 1981).

Roemer *et al*. (1993) exposed Male Sprague Dawley rats by inhalation to 0, 0.2 or 0.6 ppm acrolein for 6 h per day on one or three successive days. Nasal and tracheal epithelial and free lung cells were analyzed for proliferative responses using 5-bromodeoxyuridine (BrdU) labeling to identify DNA synthesizing cells. A single exposure to acrolein increased the DNA synthesizing cells 3-fold. After three exposures the increase was distinctly lower. All sites analyzed showed approximately the same concentration/response pattern. Since significant changes in cell proliferation were detected at 0.2 ppm acrolein, it is a LOAEL for this experiment.

Acrolein depletes glutathione (GSH) and other free thiol groups both in vitro and in vivo (WHO, 1992). Exposure of rats to a concentration of 11.4 mg/m³ for 3 hours caused irreversible depletion of GSH in the nasal mucosa. In addition, ^{14}C-labeled acrolein has been shown to bind irreversibly to sulfhydryl groups on cytochrome P450 in rats (WHO, 1992). The binding of

acrolein to sulfhydryl groups is localized to the area of contact (e.g., nasal membranes or lung epithelium), and is not a systemic effect (WHO, 1992).

VI. Reproductive or Developmental Toxicity

In rats, acrolein can induce teratogenic and embryotoxic effects when administered directly into the amniotic fluid, or when added to cultured rat embryos (ReproText, 1999; Slott and Hales, 1986). Additionally, acrolein injected into chicken embryos resulted in embryotoxicity and some teratogenic effects at moderate to high doses (0.001-0.1 mg/egg) (Chhibber and Gilani, 1986). However, intravenous exposure to 3 mg/kg in pregnant rabbits showed no developmental effects in the offspring (WHO, 1992). Based on this latter study, the World Health Organization (1992) concluded that human exposure to acrolein was unlikely to affect the developing embryo.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.09 ppb (0.19 μg/m³)

Study	Darley *et al*., 1960
Study population	36 healthy human volunteers
Exposure method	5 minute exposures to 0.06 ppm; carbon-filter respirators worn during exposure
Critical effects	subjective reports of eye irritation
LOAEL	0.06 ppm
NOAEL	not observed
Exposure duration	5 minutes
Extrapolation to 1 hour	$C^n * T = K$, where n = 1 (Ten Berge *et al*., 1986)
Extrapolated 1 hour concentration	0.005 ppm (5 ppb)
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	0.09 ppb (0.19 μg/m³)

Only volunteers without a prior history of chronic upper respiratory or eye problems were included in the study. Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. There is significant uncertainty in this calculation because of the lack of a NOAEL and the short exposure duration (5 min) in the study.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Forty-six human subjects (21 male and 25 female) were exposed to 0.3 ppm (0.69 mg/m³) acrolein for 1 hour (Weber-Tschopp *et al*., 1977). Effects included significant irritation of the eyes, nose,

and throat. A decrease in respiratory rate of 10% was evident in 47% of the subjects after 10 minutes of exposure. Based on this information the National Academy of Sciences decided that the previous EEGL of 0.2 ppm was not sufficiently protective, and it was changed to 0.05 ppm (0.115 mg/m^3). The NAS-EEGL for acrolein was determined by an expert panel and the details governing the selection of a margin of safety are not presented by NAS. Lack of data on 1-hour exposures of humans to lower concentrations of acrolein prevented NAS from deriving a definitive EEGL for a 1-hour exposure. Therefore, no recommendation can be made.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

LC_{50} data in mice, guinea pigs, rabbits, and rats ranged from 8-25 ppm (18.4 - 57.5 mg/m^3) acrolein (Carpenter *et al*., 1949; Pattle and Cullumbine, 1956; Kruysse, 1971). Based on these animal lethality studies, a value of 3 ppm (6.9 mg/m^3) was chosen by AIHA as the life-threatening level (AIHA, 1989). The methodology employed by AIHA to develop the margin of safety for the ERPG-3 for acrolein is not presented in the ERPG document. NIOSH (1995) lists a revised IDLH of 2 ppm based on several reports of acute inhalation toxicity in healthy humans for exposure periods of 10 minutes or less to 1.8-8 ppm acrolein. There is no formal protocol for its derivation and no consideration of sensitive subpopulations. Therefore, no recommendation can be made for a level protective against life-threatening effects.

VIII. References

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